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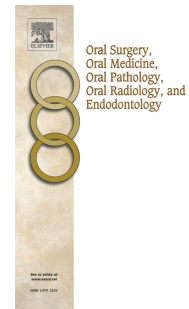
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Oral Submucous Fibrosis: A review of the current management and possible directions for novel therapies

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Abstract

This literature review addressed the tried out interventions for the management of oral submucous fibrosis. The literature supports the use of several medical interventions, including micronutrients, anti-oxidants, proteolytic enzymes, immune modulators (mainly steroids), and agents to promote blood flow. However, the numbers of reported randomized controlled trials are limited. Therefore, no recommendation can be made for any specific intervention. Until now, no single molecular pathway has been identified that is neither necessary nor sufficient for the development of fibrosis. This has been a bar for any molecular targeted therapies. Because areca nut (an ingredient of betel quid) plays a major aetiologic role in the causation of OSF cessation of areca nut use remains pivotal in the management of this disorder.

Introduction

Studies on the natural history of oral submucous fibrosis (OSF) show that it is an insidious fibrotic disorder affecting the entire oral mucosa that progresses with time. Aetiology, pathogenesis, clinical presentation and pathology of OSF have been reviewed in three other publications on this topic in this series ¹. A wide range of treatments have been advocated for the treatment of OSF, ranging from habit control (ie cessation of areca nut use), physical therapy, to medical and surgical interventions. Often a combination of these strategies is used and so far an evidence-based management has not emerged from these various trials. This paper highlights the limitations of these reported therapies and makes recommendations for future trials for the management of OSF.

Habit intervention

Epidemiological data from several populations has confirmed that areca nut is the major cause of OSF. Cessation of areca nut consumption by regular users remains the most vital step in the management of OSF. Areca nut is the fourth most addictive substance known to man and a strong dependency to areca nut by regular users was initially reported following

the work of Winstock et al who applied adapted versions of dependence scales that were designed for substances other than betel quid such as opioids.² Later authors have developed, and provided validation for an instrument designed specifically for measuring betel quid dependence: the Betel Quid Dependence Scale (BQDS).^{3,4,5,6} Chen et al devised a Self-reported Screening Test for identifying an Areca quid Abuser (SSTAA) among Taiwanese. They selected 11 questions for self-rating abuse and a score of 4 or more in these 11 questions identified an areca quid abuser.⁷

In a literature search conducted by us no reports were found that looked at the effect of habit control ie cessation of areca nut habit alone as a primary intervention. The methodology of other interventional studies included the advice to quit the habit, although only few of these studies described specific measures for cessation. For example, a study conducted in Sri Lanka the subjects were given brief advice on areca nut cessation and dental cleaning at baseline to remove staining and then re-examined at follow-up visits for any new staining⁸. No serum markers for metabolites of areca nut were utilized as evidence of cessation. The effect of cessation was neither validated nor measured. One limitation faced by researchers / clinicians conducting cessation activities is that no active agent is yet available as a suitable replacement product to areca nut to assist users to quit the habit. However, the provision of advice and follow up requires a systematic approach by the care givers

Medical interventions

Many observational or retrospective studies that included a medical intervention for the management of OSF are listed in Table 1. Various medical interventions used are highlighted and their alleged mechanisms of action are briefly stated. These agents were delivered in several modes: orally for systemic absorption, intra-lesionally, or topically, as single agents or as a combination of agents. In summary, 15 studies used a single agent, and

the rest studied a combinations of agents. In this review we cite the studies that used the use of nutrients, micronutrients and/or anti-oxidants, 21 studies included the use of immunomodulatory agents that reduced the inflammatory component, principally injected corticosteroids (16 studies). 19 studies included the use of proteolytic enzymes to reduce fibrosis of which 7 used hyaluronidase. Several studies included agents to promote blood flow.

Nutritional supplements

Earlier studies had identified nutritional deficiencies as a potential causative factor in OSF⁹. Other reports have shown that many subjects diagnosed with OSF were deficient particularly in iron and B vitamins¹⁰. In view of these findings several authors have attempted nutritional supplementation as a measure of adjunctive treatment of OSF. Among the supplements used, vitamins A, B complex, C and E have been tried alone or in combination with other agents^{11, 12, 13, 14, 15, 16}. The rationale for their use is to correct any deficiency states and promote normal cellular processes present in health, to improve the epithelial atrophy noted in OSF, particularly the generalized tongue depapillation. Superficial ulceration is often noted in OSF subjects and these supplements are thought to improve tissue healing. In a study conducted in Pakistan multiple micronutrient supplementation was shown to improve symptoms of OSF and mouth opening in an open trial¹⁵. 41% of subjects showed improvement in mouth opening. Though symptom improvement was achieved, it is unlikely that nutritional supplementation alone contribute to any improvement of fibrosis in this condition. Among minerals, zinc,^{12, 15, 16} magnesium,¹⁵ selenium¹⁶, manganese^{15, 16} and iron¹¹ have been tried (mostly in combinations of two or more minerals) as therapeutic agents. Zinc may play a role in chelating copper and correct the imbalance of excess copper proposed as a causative factor¹. Kumar and Sharma have shown a beneficial effect of oral zinc alone in treating OSF¹².

Anti-oxidants

One of the pathogenic mechanisms of areca nut has been attributed to the generation of reactive oxygen species, free radicals and peroxidases.¹⁷ Based on this hypothesis several authors have tried various naturally occurring or synthetic anti-oxidants. These include, beta carotene, lycopene, tea pigments, aloe vera, curcumin and spirulina.

Beta carotene was used as an antioxidant in one trial arm described by Jirge et al.¹⁶. Following systemic administration for 15 weeks an improvement of mouth opening by 6.7% was recorded.

Lycopene is a red coloured carotenoid predominantly accumulated in tomatoes as well as in other pigment containing vegetables and fruits. Lycopene has been reported to be beneficial in the management of other oral potentially malignant disorders eg. oral leukoplakia and lichen planus^{18,19}. The effectiveness of lycopene has been tested in two randomized controlled studies. Kumar et al.²⁰ recruited 83 participants who received either oral lycopene (n=21; group A), oral lycopene with intralesional corticosteroids (n=19; group B) or an oral placebo (n=18; group C). The two-month intervention period was completed by 58 people. Objective measurement of mouth opening was reported to be significantly improved with an average increase of 3.4mm, 4.6mm and 0mm for groups A, B and C, respectively. The increases were maintained at 3 and 6-months follow-up. All patients who took lycopene reported relief from burning sensations within 2 weeks, whereas only one patient from the placebo group reported a similar improvement. One other randomized single blind trial testing the effectiveness of lycopene, was conducted in Maharashtra, India²¹. 92 participants were enrolled, 46 subjects were given 8 mg lycopene daily and the rest were given a placebo tablet for 3 months and followed up for further 2 months. Significant improvement was reported in mouth opening, mean (SD) 4.48 mm (3.65) in the lycopene

group compared with 1.13 mm (1.6) in the control group, and 31% experienced a complete improvement in burning sensation vs 7% in the control group.

Tea pigments contain oxidised products of polyphenols, derived from tea leaves. Among patients with haematinic deficiencies at baseline when supplemented with tea pigments together with vitamins A, B, C and D the authors reported an increased mean mouth opening of 7.9 mm in 7/12 OSF patients in China²². The authors suggested that, in addition to their anti-oxidant properties, the tea pigments are likely act by improving the microcirculation in these patients.

Radix *Salviae miltiorrhizae* (danshen), the dried root of *Salvia miltiorrhiza* Bge is very important and popular in traditional Chinese medicine. Salvianolic acid B (Sal-B) is the most abundant and bioactive member of the hydrophilic components in Danshen. Sal-B contains seven phenolic hydroxyls which have been found to be closely related to redox potentials and/or antioxidant activities²³. Recently, the efficacy of salvianolic acid B (SA-B) combined with triamcinolone acetonide in the treatment of oral submucous fibrosis was tested²⁴. A net gain of mouth opening by 5.5 mm was reported in the SA-B group in 20 weeks but this relapsed to 3.5 in 44 weeks. The exact antifibrosis mechanism of SA-B is not known.

Spirulina, a blue green algae rich in carotenoids and other micronutrients which have chemopreventive potential was used in combination with other agents to test its effectiveness in three trials^{25, 26, 27}. In one study, the patients on Spirulina showed significant clinical improvement in mouth opening and ulcers/erosions/vesicles compared to topical aloe vera²⁵, in reducing burning sensation compared with pentoxifylline²⁶, and in both mouth opening and burning sensation compared with biweekly intralesional steroid injection of Betamethasone (4 mg/ml for 3 months)²⁷.

In a randomised controlled trial, 10 patients with OSF received a topical application of aloe vera gel (5mg applied 3 times daily to the buccal mucosa for 3 months) and were compared with 10 patients who received antioxidant capsules twice daily ²⁸. In the experimental arm a 55%-65% reduction in burning sensation was noted when measured by a VAS scale. An improvement of 4.3-7mm in mouth opening was also reported.

In a further randomised trial aloe vera gel was tested as an adjunct to medicinal (injection of a mixture of hyaluronidase and dexamethasone) and surgical approaches in the treatment of OSF ²⁹. 60 patients were randomized into the medicinal and surgical groups, and within each group (n=30), half received the gel treatment. Additional improvement in both mouth opening and burning sensation were found in those receiving the aloe vera.

Effect of curcumin was tested in a randomised clinical trial in comparison to intra-lesional steroid injections ³⁰. The experimental arm (n=20) received curcumin by oral administration of 2 tablets of Turmix (each film-coated tablet containing 300 mg C. longa and 5 mg piperine) given once daily for a period of 3 months. The control group received weekly intralesional injections of 4 mg dexamethasone and 1500 iu of hyaluronidase. Mouth opening improved by 3 mm and the burning sensation improved completely in the curcumin group.

In a further RCT, a combination of curcumin and turmeric oil was tested by Das et al ³¹. Curcumin 1g per day was given in two divided doses, and a second group was given 12 drops of turmeric acid to hold in mouth and swallow twice daily. A control group received multivitamins 500 mg twice daily. Patients were followed up monthly for 6 months. Complete relief of pain was reported in both experimental groups after one month's treatment. A mean increased mouth opening of 0.87 cm was noted in both test groups significantly better compared with 0.18 cm in the control group..

Immunomodulation using steroid preparations (topical and intra-lesional)

Various steroid preparations have been tested in an attempt to reduce profibrotic inflammation, and to enhance pro-fibrolytic immune-mediated pathways. In Indian studies, the use of steroids has been the most widely adopted approach for the treatment of OSF. The agents used have included betamethasone and triamcinolone acetonide as topical agents^{11, 13}, and hydrocortisone, methylprednisolone (20mg/0.5ml), dexamethasone, triamcinolone diacetate used for intra lesional injections^{32, 12, 33, 8, 34, 35, 11, 13, 36, 37, 38, 39, 30, 20, 29, 24 40}. Topical steroids (see Table 1) may relieve the early symptoms of inflammation and mucositis experienced by OSF subjects but have not shown any efficacy in reversing fibrosis. The authors report better results derived by intra-lesional injections, although it is alleged that repeated needle-stick trauma may cause additional scar tissue formation⁸.

Other immunomodulators

Levamisole was tested in one RCT. The 45 participants reported by Jirge et al¹⁶. were divided equally between three study groups: oral levamisole (group I), an oral antioxidant [Antoxid[®]] – containing beta carotene, selenium oxide, zinc sulphate, manganese and copper](group II), or oral levamisole with antioxidant (group III). On conclusion of the intervention period (approximately 15 weeks) there were improvements of mouth opening of 7.1%, 6.7% and 8.0% in groups I, II and III, respectively. These gains were maintained on further evaluation two months later. There was also a significant reduction in burning sensations in all study groups.

Probiotic agents, such as immunised cows milk prepared by immunization of cows with human intestinal bacteria has been proposed as a method of immunomodulation. The authors

reported an increase on mouth opening in 69% of their subjects by >3 mm but this study has not been reproduced elsewhere⁴¹.

Biogenic stimulators

Aqueous extracts of human placentas have been used as a biogenic stimulator in several studies as a way of altering collagen synthesis^{34, 35, 42, 43, 14} (see Table 1).

Cytokines

Among an immigrant Asian population in London, interferon gamma (IFN γ) was used to downregulate fibroblast proliferation as a treatment of OSF⁴⁴. 15 injections of 50 ug IFN γ was injected intralesionally twice a week for 8 weeks and followed up to 6 months. The authors noted some improvement in OSF but the study was uncontrolled and was confounded by simultaneous use of physiotherapy.

A COX-2 inhibitor has been tried as a mucoadhesive film (valdecoxib) applied to the buccal mucosae in a pilot study as a proof of concept to use long acting topical agents⁴⁵.

Enzymes and fibrinolytic agents

Proteolytic enzymes are known to breakdown the inappropriate connective tissue fibrosis. Cross-linking of collagen has been observed in OSF as a pathogenic mechanism contributing to the limitation of mouth opening in advanced cases. Several agents have been tested to promote fibrolysis, the most common of which is hyaluronidase^{34, 35, 11, 13, 32, 29, 40} which, when injected, is known to breakdown the intercellular cement substances. Krishnamoorthy et al in Bangalore, India between 2002 and 2004 enrolled 50 patients randomized to two groups. Group 1 received an oral tablet of colchicine 0.5 mg twice daily and 1500 IU hyaluronidase mixed in 1 ml lignocaine (0.5 ml) injected intralesionally into the buccal

mucosa. Group 2 received hyaluronidase as in group 1 and in addition 0.5 ml of hydrocortisone acetate 25mg/ml to each buccal mucosa once a week for 12 weeks. Both groups received habit intervention. Significant improvement of symptoms were reported in both study groups⁴⁶. Other agents include papain as a topical agent, and both collagenase and chymotrypsin used as intralesional injections. Collagenase is a lysosomal enzyme capable of degrading various esters that are involved in cross linking of the cement substance. Chymotrypsin is a proteolytic enzyme (Serine protease) acting in the digestive systems of many organisms. It facilitates the cleavage of peptide bonds. Some improvement of symptoms have been reported by various Indian authors^{14, 39, 37, 35}.

46

Vasodilators

The rationale for the use of a peripheral vasodilator, is based on the assumption that it may relax and dilate the blood vessels in the stromal tissues, ensuring greater blood supply to the ischemic tissues and helps the nutritional and therapeutic agents to reach the affected tissues. The agents tested include pentoxifylline^{47, 48}, nylidrin hydrochloride⁴⁹, buflomedial hydrochloride¹³ and Danxuan Koukang (DXKK)⁵⁰, and isoxsuprine³⁶ (see Table 1).

Pentoxifylline, generally marketed for intermittent claudication, is known to have a gamit of properties that may alter the course of wound healing. Connective tissue disorders may respond to pentoxifylline with an increase in fibroblast collagenases and decreased collagen, fibronectin, and glycosaminoglycan production. Fibroblast responsiveness to tumor necrosis factor is also diminished by this agent⁵¹. Pentoxifylline was used in two RCTs^{47, 48}. In the earlier trial, twenty-nine participants were divided into two groups that took either oral pentoxifylline or multi-vitamins. All those enrolled completed the 7 month study period. The authors reported statistically significant improvements in the oral pentoxifylline group (n=14) compared to controls with respect to both the objective criteria (mouth opening, tongue

protrusion and relief from circum-oral fibrotic bands) and the subjective criteria (intolerance to spices, burning sensations, tinnitus, difficulty in swallowing, and difficulty in speech).

A later study by Mehrotra et al ⁴⁸, 32 patients were given pentoxifylline for a period of 7 months, administered for the initial 30 days at a reduced dosage of 400mg twice daily and then increased to 400mg three times tablets daily for 6 more months as per the earlier study. The placebo group (n=30) was given multivitamin therapy. The authors reported 10 mm improved mouth opening with pentoxifylline compared to 6 mm with multivitamins.

In a further study a vasodilator, isoxsuprine, combined with physiotherapy, was compared to intralesional injections of dexamethasone with hyaluronidase and physiotherapy or physiotherapy alone on the symptoms of OSF ⁴⁰. The authors reported the outcome after 6 weeks of treatment and then again at the end of the 4 months follow up period. Both isoxsuprine and dexamethasone with hyaluronidase treatments significantly alleviated burning sensation and increased mouth opening by approximate 3 mm,

Evaluating outcome measures

Outcome measures reported in intervention trials on OSF are highly variable both in the type and the manner in which they were measured. In terms of objective measures, mouth opening (generally measured as inter-incisal opening) appears to be the most frequently measured outcome across all studies, although the level of reliability (e.g. validation of measurements) is not clearly defined. Instruments have been introduced that enable the clinician to accurately measure the inter-incisal distance. Other objective measures include changes in tongue movement (ie ability to protrude), degree of suppleness of the tissues, amount of blanching of the mucosa, presence of ulceration/vesicle formation, and amount of dorsal tongue papillation, although the methodology for measuring these other objective outcomes is poorly defined in many research studies and are of questionable reliability. In terms of subjective

measures, oral burning/pain is the most consistently measured subjective outcome, although very few studies reported the outcome using validated pain assessment instruments, such as a visual analogue pain rating scale (VAS). Other subjective measures include change in taste, oral dryness, and ability to chew, swallow, or speak. None of the studies used validated instruments evaluating quality of life of subjects with OSF, nor could we find any such instruments in the published literature.

Physical exercise

Cox and Zoellner enrolled 54 Nepali subjects into 3 groups: physiotherapy, injections with a combination hyaluronidase/steroids, and a control group. After 4 months, subjective and objective measures were compared to baseline. The physiotherapy group showed a significant increase in opening but had no superior effect on subjective measures³².

For subjects with advanced OSF ultrasound therapy has been tested. Ultrasonic tissue heating is likely to increase local tissue temperature, increased local circulation of blood flow and possible tissue disruption of cross linked collagen. Pal et al reported an improvement of symptoms in 50% of their cases when treated by ultrasonography⁵². (see Table 2)

Surgical treatment

There is an exhaustive literature on surgical excision of bands, coronectomy and temporal muscle myotomy to release the fibrosis among patients not responding to conservative treatment or for advanced cases of OSF (Table 3). Instead of cold knife surgery the use of CO2 or KTP-532 or Diode laser⁵³ has also been reported for removal of fibrous bands.

Reconstruction with tissue flaps from various donor sites has been undertaken. It is not intended to review this literature in full as surgical interventions are covered elsewhere^{13, 54}. Various grafting techniques include the use of buccal fat pads, tongue flaps, nasolabial flap,

and radial forearm flaps^{55, 38, 56, 57, 58, 59, 60, 61, 62, 63, 59, 64, 56, 65, 66, 67, 68, 69, 70, 68, 63}. Artificial grafts that promote tissue regeneration have also been advocated in reconstruction of defects following surgery⁷¹. Continued physical therapy is advocated to reduce relapse following surgery. A randomized trial comparing a nasolabial flap with a radial free forearm flap was reported recently⁷². 60 patients with OSF were recruited, 30 to each arm of the study. Stick exercises were encouraged for all patients from day 1 following surgery. None of the patients experienced necrosis of flaps and results for the 50 subjects were available. Both surgical techniques achieved good mouth opening but average shrinkage of about 5 mm was noticed in patients in the late post operative period. Mean increase in mouth opening was greater in patients receiving the radial free forearm flap compared with nasolabial flap (18.96 mm vs 15.16 mm).

Randomized Controlled Studies

A Cochrane review⁷³ and a later published systematic review⁷⁴ identified three medical interventions with an RCT design to study the effectiveness of systemic therapies on OSF: pentoxifylline⁴⁷, lycopene²⁰ and levamisole with anti-oxidants¹⁶. These trials were run at a single center, were randomized but the observers were not blinded in reporting outcomes. There was one other prospective controlled study that lacked randomization³⁷. Since the publication by Kerr et al⁷⁴ several medical interventions with a RCT design have been added to the literature testing lycopene, colchicine and hyaluronidase^{21, 46}, aloe vera^{28, 29}, and the vasodilators pentoxifylline⁴⁸, isoxsuprine⁴⁰, and Salvianolic acid²⁴. Curcumin and turmeric oil³¹ has also been used in one open label trial.

On the application of physical exercise and comparison of surgical techniques there is a single RCT in each category^{32, 72}.

A working group of the WWOM V reanalyzed the published data from four RCTs (completed before 2011) using the GRADE criteria and identified significant limitations with

each trial and challenged the conclusions reached by the authors. The studies published after 2011 appear to have similar limitations to these previously reported RCTs.

Future studies

Based on the extensive literature reviewed here the authors would like to propose potential therapies that need further study. It is important to bear in mind cost considerations of any proposed therapies in view of the socioeconomic status of the affected population in low to middle income countries. Taking into account the chronicity of the disease, patient compliance also may be sub-optimal for undergoing aggressive therapies. Naturally occurring compounds with anti oxidant properties eg. curcumin, aloe vera and tea pigments therefore have a great appeal. These agents in various formulations need to be tested in large clinical trials in Asia.

When topically applied medications are used for treatment of OSF, poor permeation and absorption is likely and may limit efficacy. Recently developed novel muco-adhesive buccal films when tested *in vitro* appear to facilitate the delivery the drugs to local sites effectively⁴⁵.

Trials testing antioxidants have shown some improvement in both mouth opening and burning symptoms. Further trials are indicated in larger populations.

Recently *Clostridium histolyticum* collagenases (Xiapex) has been licensed for the treatment of fibrotic conditions such as Dupuytren's contracture. It contains collagenase isolated from the bacterium *Clostridium histolyticum*. The enzyme has a high affinity to digest collagen (particularly class 1 and 111) and to cleave insoluble triple helical collagen. A double-blind randomized study has confirmed its efficacy in Duputrene's contracture⁷⁵. However, the cost of this new enzyme may preclude its availability in low-income countries.

Transforming growth factor β (TGF β) plays a specific role in regulation of ECM by regulating the synthesis and degradation of specific ECM components. Upregulation of TGF β has been demonstrated in OSF and has been proposed to play a pivotal role in the aetiopathology¹. Aberrant expression of this growth factor has also been reported in keloids, atherosclerosis, pulmonary and liver fibrosis and scleroderma⁷⁶. Imatinib is thought to affect fibrotic pathways by selectively interfering with TGF β signaling pathways⁷⁷. Imatinib has been used as an antifibrotic drug for experimental treatment of scleroderma⁷⁸ and may have a role in placebo-controlled studies in OSF.

Pirfenidone has well-established antifibrotic and anti-inflammatory properties in various *in vitro* systems and animal models of fibrosis. A number of cell-based studies have shown that pirfenidone reduces fibroblast proliferation, inhibits TGF β stimulated collagen production. Pirfenidone has been evaluated in a phase III trial for patients with idiopathic pulmonary fibrosis (IPF). Other potential candidates include Simtuzumab developed by Gilead Sciences, Inc. –(humanized monoclonal antibody targeting the human LOXL2 protein). The LOX enzyme is known to be upregulated in OSF⁷⁹. Simtuzumab is currently being evaluated in a phase II trial for patients with IPF. A recent group has hypothesized that hyperbaric oxygen may contribute to treat OSF as it decreases the expression of hypoxia-inducible factor HIF and simultaneously increases the vascular VEGF expression and angiogenesis⁸⁰

Recent reviews on molecular mechanisms underlying OSF have revealed possible molecular targets that may be used in interventions.^{92,93} Targeted therapies could be designed using these novel findings.

Conclusions

OSF remains refractory to most chemopreventive or other systemic medical therapies tried so far in the past 3 decades. Placebo-controlled trials all show some improvement but

the sample sizes have been small and analyses of trial data have not been robust. More trials are needed before the benefit of these already tried out medicines can be confirmed.

Furthermore, promising novel antifibrotic drugs used in other systemic conditions have not been tested in this population.

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Table 1: Medical Interventions

Group	Rationale	Examples of Interventions		Dosage /route	references	
Nutrients, micronutrients	Correct deficiency states and promote normal cellular processes present in health that help to protect against adverse events including carcinogenesis	Systemic	Vitamins A, B complex, C, D & E plus minerals iron, zinc, magnesium and others given singly or in combination		11 12 38 13 14 81 16 , , , , , ,	
Anti-oxidants	Cells are protected against oxidative stress by interacting with an antioxidant	Systemic Topical	Glucosidorum tripterygii totorum, vitamins A & E, nicotinic acid		36	
			Lycopene	Systemic; 8 mg daily	20 21 ,	
			Tea pigments		22	
			Salvianolic acid		23	
			Aloe Vera	5mg applied 3 times daily	28 29 ,	
			Curcumin	300 mg C. longa and 5 mg piperine or 1g per day or 1g per day	30 31 ,	
			Spirulina	500 mg twice daily	25 26 27 ,	
Biogenic stimulation	Homograft stimulates favourable metabolic processes that promote non-fibrotic tissue regeneration	Intralesional injections	Placental extract		43 34 35 42 14 , , , ,	
Proteolytic enzymes	Proteolytic enzymes breakdown the inappropriate connective tissue fibrosis	Intralesional injections	Papain (cysteine protease) with keratolytic action of urea:		14	
			Collagenase		37, 39	
			Hyaluronidase	1500 IU mixed in 1 ml lignocaine	34 35 11 13 32 , , 33 46	
			Chymotrypsin		35	
Immune modulation	Immune modulation that diminishes pro-fibrotic inflammation and enhances pro-fibrolytic immune-mediated pathways	Topical	Corticostero id	Betamethasone	Topical	11
				Triamcinolone acetonide	Topical	13
		Intralesional injections	Corticostero id	Dexamethasone		34 35 11 13 36
				Triamcinolone diacetate		37 11 38 39 33 , , , ,
				Methylprednisolone	20mg/0.5ml	8
				Betamethasone	0.5 ml of 4 mg/ml	20
				Hydrocortisone	0.5 ml of 25mg/ml	32 12 33 46 , , , ,
			Other	Interferon gamma (IFN-γ)	Intra-lesional 50 ug twice a week	44
				Colchicine	0.5 mg twice	46

					daily	
		Systemic	Levamisole			16
			Cows milk immunised with multiple human intestinal bacteria			41
Promotion of blood flow	Promote blood flow to ischaemic tissues via multiple mechanisms including vasodilatation and mild anti-coagulant effects with other biological actions including immunomodulation and anti-oxidant functions	Systemic	Pentoxifylline	400mg bd or tds		47
			Isoxysuprine			40
			Nylidrin Hydrochloride			49
			Buflomedial hydrochloride			13,

Table 2: Physical Therapy and Surgical Interventions

Group	Rationale	Examples of Interventions		references
Physical therapy	Modify tissue remodelling through promotion of physical movements and localised heat	Physiotherapy	Physical exercise regimen (including post-surgery)	13, 32
			Splints or other devices (including post-surgery)	82 83 84 85
			Microwave diathermy	86 14
Group	Rationale	Examples of Interventions		references
Surgical Interventions For advanced cases with severe limitation in opening, to release fibrous banding.		Laser excision		87 83 53 88 89
		Coronoidectomy and muscle myotomy		90 68
		Excision & flap procedures	Buccal fat pad	91 92 57 58 59
			Tongue flap	55 60
			Nasolabial flap	61 62 72 63 59
			Superficial temporal fascia flap	64
			Forearm free flap	56 65 66 67 68
			Palatal island flap	69
			Anterolateral thigh flap	70 68
			Platysma myocutaneous muscle flap	63
		Excision and grafts/stents	Split thickness skin graft	93 13 94
			Amnion graft	13
			Artificial dermis graft	71
			Collagen membrane	95
			Stents	84 94

Statement of clinical relevance

The management options for oral submucous fibrosis remain unclear. No single effective therapy has been described. This review identifies gaps in our knowledge to encourage further research to help in the development of targeted therapies.